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EXAMINER	
KWON, BRIAN YONG S	
ART UNIT	PAPER NUMBER
1614	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/760,062	SHANKAR ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *3 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-23 and 25-38* is/are rejected.

7)☒ Claim(s) *1-2 and 27-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/22/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Response to Restriction Requirement Acknowledged

1. Applicant's election, with traverse, with the Group III along with compound 129 and cancer as the elected species is acknowledged.

Applicants traverse the restriction requirement on the grounds that there would be no burden in searching the entire groups. This argument is not persuasive, as claimed invention would be distinctive, each from the other for the reason of the record. Furthermore, the search of the entire groups in the non-patent literature (a significant part of a thorough examination) would be burdensome. Therefore, the requirement is still deemed proper, and made Final.

2. With respect to the applicant's argument that claims 2 and 28 should also be included in Group III, the examiner recognizes that such argument is persuasive. Accordingly, claims 2 and 28 are rejoined with Group III invention and examined to the extent that they read on the elected invention.

3. Claims 1-2, 4-23 and 25-38 read on the elected invention. Claims 3 and 24 are withdrawn from further consideration by the examiner as being drawn to non-elected invention.

4. The elected species compound 129 is free from prior art, search has been extended to compound read on elected invention (having Edg7 receptor inhibitory activity, for example compound 126). The claims have been examined insofar as they readable to the searched compound.

Priority

5. It is noted that this application appears to claim subject matter disclosed in prior Application No. 60/440,336, filed January 16, 2003. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition

must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Objections

6. Claims 28 and 33 are objected to because of the following informalities: "selected from" is improper Markush-type language. "selected from" should be corrected as "selected from the group consisting of". Appropriate correction is required.

7. Claims 29-32 are objected to as being incomplete. No structure and definition of compound of formula I or II are depicted in claims 29-32. For the examination purpose, "the formula (I) or (II)" is interpreted as the compound of the formula (I) or (II) in claim 1 or 2.

8. Claim 27 is objected to because of the following informalities: "comma" is missing after "HUVEC cells".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 4-23 and 25-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing or activating the specific biological activity (e.g., calcium mobilization, VEGF synthesis or IL-8 synthesis) or treating the specific cancer with the specific compound represented by the formula (III), does not reasonably provide enablement for "modulating an Edg-7 receptor medicated biological activity...", "treating or preventing cancers..." or "treating cancers..." or "compound represented by the formula (I), (II) or (III)". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

The instant claims are drawn to a method for modulating an Edg-7 receptor mediated biological activity or treating or preventing "cancers..." comprising administering a compound of formula (I), (II) or (III).

Websters II Dictionary defines the term "modulate" as "to adjust or adapt to a certain proportion; to pass gradually from one state to another", "prevent" as "anticipate or counter in advance, to keep from happening" and "inhibit" as "to prevent; to prohibit".

The interpretation of the instant claims, drawn to "a method of modulating an Edg-7 receptor mediated biological activity..." allows for the inhibition (down-regulation), stimulation or enhancement (up-regulation) and/or mixed up and down regulation of an Edg-7 receptor mediated biological activity, whereas the interpretation of the instant claims, drawn to "a method of treating or preventing "cancers..." allows for the complete cure and eradication or total elimination of "cancers..." or treatment of any cancers mediated through Edg-7 receptor by the administration of said compounds represented by the formula (I), (II) or (III).

With respect to the scope of enablement for "modulation" (inhibition or prevention) of Edg-7 receptor mediated biological activity or "prevention" of "cancers, acute lung diseases, acute inflammatory...",

Similarly as discussed above, the interpretation of instant claims includes not only the modulation (e.g., inhibition and/or activation) of Edg-7 receptor mechanism, but also the

treatment or prevention of any diseases or conditions associated or involved with Edg-7 receptor mechanism by administering the compounds represented by the formula (I) or (II).

There are no known compounds of similar structure which have been demonstrated to prevent or cure any diseases or biological activities by Edg-7 receptor mechanism. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merit. For example, there is no known cure for cancers or cardiovascular diseases. The true fact of the state of the art is illustrated succinctly in the ("NIH Heart Disease & Stroke Research: Fact Sheet", American Heart Association, 2004; "Cardiovascular Disease: Treatment for Stroke", Stanford Hospital & Clinics, 2003; "Heart Disease", Charlotte E. Grayson, WebMD, 2004; "Acute Congestive Heart Failure", Thomas N. Levin, Postgraduate Medicine, Vol. 101, No. 1, 1997; "Baylor, St. Luke's study uses gene therapy as pancreatic cancer", April Sutton, www.bcm.edu, 2006; "Drugs hold promise in kidney cancer fight", Marchione et al., www.ledger-enquireer.com, 2006). Thus, it is not understood how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" or completely cure or eradication effect.

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmacy art is high. The specification does not provide any competent evidence or disclosed tests that are highly predictive for the preventive utility of the instant compounds.

The specification discloses compounds 101, 111, 117, 119, 126, 129, 131, 133, 135 and 137 as the suitable examples of the invention and provides assays in vitro to test compounds that compounds 105 and 107 exhibit Edg-7 receptor inhibitory properties (Examples). However,

there is no demonstrated correlation that the tests and results apply to the claimed preventive utility embraced by the instant claims.

Since the efficacy of the claimed compound(s) in preventing the claimed conditions (for example cancers or cardiovascular diseases) mentioned above cannot be predicted from a priori but must be determined from the case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to use the invention commensurate in scope with the claims.

With respect to the scope of enablement for the treatment (or prevention) "Edg-7 receptor mediated biological activity", "cancers...cardiovascular diseases" or "cancers",

The relative skill of those in the art of pharmaceuticals and the unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5(BDAI

1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art; In re Wright, 9999 F.2d 1577, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of treating or preventing "Edg-7 receptor mediated biological activity", "cancers, acute lung diseases, acute inflammatory exacerbation..." or "cancer" prior to filling of the instant invention was an unpredictable art.

The scope of the instant invention is extremely broad. The scope of the instant claims encompasses prevention (complete thwarting or warding off illness or total elimination or eradication of disease) or treatment of multiple complex disorders that may have unrelated manifestations including cancers (e.g., ovarian, peritoneal, endometrial, cervical, breast, colorectal, uterine, stomach, small intestine, thyroid, lung, kidney, pancreas and prostate cancer), acute lung diseases, adult respiratory distress syndrome, asthma, cutaneous burns, transcorneal freezing, cardiovascular diseases (e.g., coronary artery disease, heart valve disease, arrhythmia, heart failure, stroke, shock, endocarditis, diseases of the aorta and its braches, disorders of the peripheral vascular systems, congenital heart diseases, angina (particularly chronic, stable angina pectoris), cardiomyopathy, restenosis, ischemic disease, pulmonary edema associated with acute myocardial infarction, thrombosis, platelet aggregation, platelet adhesion, pulmonary thromboembolism, cerebral thromboembolism, arteriovenous fistula, atheroembolism, etc...).

Although the instant invention links Edg-7 mechanism to the pathophysiology of multitude of disease as discussed above, it is not known yet that a single underlying mechanism ties together all of the seemingly unrelated manifestations. Therefore, the skilled artisan would turn to undue amount of trial and error to find out which disease or condition would be response to the administration of said compounds having Edg-7 receptor modulating activity.

The specification discloses compounds 101, 111, 117, 119, 126, 129, 131, 133, 135 and 137 as the suitable examples of the invention and provides assays in vitro to test compounds that compounds 105 and 107 exhibit Edg-7 receptor inhibitory properties (Examples). However, there is no demonstrated correlation that the tests and results apply to the treatment of disease conditions embraced by the instant claims. Ex parte Maas, 9 USPQ2d 1746, makes clear "First, although appellants' specification describes certain in vitro experiments, there is no correlation on this record between in vitro experiments and a practical utility in currently available form for humans or animals. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to utility in humans or animals".

As discussed above, no examples exist for efficacy of a single product against all types of diseases or conditions or cancers. For example, Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different method of growth and harm the body. Also see In re Buting, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate

types of cancers'. Thus, it is beyond the skill of oncologists or pharmacologists today to get an agent to be effective against "biological activity" or "cancers..." mediated by Edg-7 receptor mechanism. As discussed in preceding comments, the existence of such a "silver bullet" is contrary to our present understanding of oncology or pharmacology.

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fishcher, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575.

As discussed above, considering above factors, especially the "sufficient working examples", "the level of skill in the art", "the relative skill and the unpredictability in the pharmaceutical art", "breadth of the claims" and "the chemical nature of the invention", one having ordinary skill in the art would have to undergo an undue amount of experimentation to practice the claimed invention.

With respect to the scope of enablement for Edg-7 receptor modulator represented by the formula (I), (II) or (III),

The specification discloses compounds 127, 129 and 131 as the suitable examples of the invention and provides prophetic examples of assay method to evaluate Edg-2 receptor involvement in calcium mobilization, VEGF synthesis, IL-8 synthesis, cell migration, inhibition of cAMP formation, and cellular proliferation (Examples).

It is generally recognized in the art that biological compounds often react unpredictably under different circumstances (Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)).

The relative skill of the artisan and the unpredictability of the pharmaceutical art are very high. To practice the instant invention to the claimed scope, applicant would have to (i) make or synthesize numerous possible compounds of the formula(s) considering the structure-activity relationship of the compounds, (ii) screen potentially suitable compounds and (iii) assay to find out which compounds are able to exhibit the desired selectivity for Edg-2 relative to other Edg receptors (particularly Edg-4 and Edg-7 receptors, and then (iv) extrapolate the test and result to the claimed therapeutic utility. In other words, the instant invention necessitates for the skilled artisan to undergo an exhaustive search for the embodiments suitable to practice the claimed invention.

Where the physiological activity of a chemical or biological compound is considered to be an unpredictable art (Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970)), the skilled artisan would have not known how to extrapolate the result provided in the instant

specification to the larger and highly varied genera of compounds that are characterized by the modulator represented by the formula (I), (II) or (III), without undue amount of experimentation.

As discussed above, given the breadth, the disparate nature of compounds that is presently claimed, the highly unpredictable state of the art where many specific differences or different physicochemical properties are existed among unrelated structural compounds or even structurally related compounds, the limited number of exemplified Edg-2 receptor antagonists and the insufficient amount of guidance present in the specification, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to make/use the claimed modulators that would be enabled in this specification (The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976))).

The examiner acknowledges that the Office does not require the present of (all) working examples to be present in the disclosure of the invention (see MPEP 2164.02). However, given the highly unpredictable state of the art and furthermore, given that the applicant does not provide sufficient guidance or direction as to how to make and use the full scope of the presently claimed invention without undue amount of experimentation, the Office would require appropriate disclosure, in the way of scientifically sound reasoning or the way of concrete

examples, as to why the data shown is a reasonably representative and objective showing such that it was commensurate in scope with and, thus, adequately enables, the use of the elected species for the full scope of the presently claimed subject matter. Absent such evidence or reasoning, applicant has failed to obviate the rejection of the instant claims under 35 USC 112, first paragraph (for the lack of scope of enablement).

10. Claim 31 is rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claim is drawn to a method for treating or preventing "a disease or condition selected from cancers...." comprising administering a compound of formula (I), (II) or (III) in combination with one or more agonists or antagonists of an Edg-7 receptor.

The instant specification only discloses agonist or antagonist of the formula I, II or III. There is/are no support(s) or reference(s) of any other Edg-7 modulating compounds other than the instant compounds of the formula I, II or III in the instant specification.

Reading the instant specification, the skilled artisan would have not known how to make/use "one or more agonists or antagonists of an Edg-7 receptor" other than the compounds of formula I, II or III. The specification provides insufficient written description provision of 35 USC 112, first paragraph, to support the genus encompassed by the claim.

Vas-Cath Inc. Mahurkar, 19 USPQ2d 1111, makes clear the "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry,

whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966(1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)* ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-2, 4-23, 25-32 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims (claims 1-2, 4-13, 15-18, 22-23, 26-28) are vague and unclear of the term "Edg-7 receptor mediated biological activity" and leave the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear. In this regard, although the specific examples (calcium mobilization, VEGF synthesis, etc...) are shown in the specification, it is considered that the meaning of the claims should be clear from the wording of the claim alone.

Regarding claim4, claim 4 recites "an antagonist". The claim is vague and unclear and leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear. What types of antagonist activity does it refer to?

Regarding claims 5-9 and 15-16, the claims recite "other Edg receptors". The claims are vague and unclear and leave the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear. What types of Edg receptors do they refer to as comparing with the compounds of the formula having Edg-2 inhibitory activity? In this regard, although the specific examples (i.e., selectivity for Edg-2 relative to Edg-4 and Edg-7 receptors) are shown in the specification, it is considered that the meaning of the claims should be clear from the wording of the claim alone.

Regarding claims 1, 2 and 36, the claims recite "substituted". The claims are vague and unclear and leave the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear. One of ordinary skill in the art could not ascertain and interpret the metes and bounds of the patient protection desired as to "substituents" encompassed thereby. Given the fact that any significant structural variation to a compound would be reasonably expected to alter its properties, e.g., physiological effects and functions, the scope of claim is indefinite as to the compound encompassed thereby. In this regard, although the specific embodiments (i.e., substituted alkyl, susbstitued alkylthio, substituted heteroalkyl, etc...) are shown in the specification, it is considered that the meaning of the claims should be clear from the wording of the claim alone.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-2, 4-23, 25-26 and 28-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Honn et al. (USP 4906646).

The claims read on method of modulating an Edg-7 receptor mediated biological activity comprising contacting a cell expressing the Edg-7 receptor with an amount of a modulator of the Edg-7 receptor represented by the formula (I) sufficient to modulate the Edg-7 receptor mediated biological activity. Further limitations include "antagonist" (claim 4); "the modulator exhibits at

least about 200 fold inhibitor activity selectivity for Edg-7 relative to other Edg receptors" (claims 5 and 15), particularly "relative to Edg-4 and Edg-2 receptors" (claims 10 and 17); "the modulator exhibits at least about 40 fold inhibitor activity selectivity for Edg-7 relative to other Edg receptors" (claim 6), particularly "relative to Edg-4 and Edg-2 receptors" (claim 11); "the modulator exhibits at least about 12 fold inhibitor activity selectivity for Edg-7 relative to other Edg receptors" (claim 7), particularly "relative to Edg-4 and Edg-2 receptors" (claim 12); "the modulator exhibits at least about 5 fold inhibitor activity selectivity for Edg-7 relative to other Edg receptors" (claims 8 and 16), particularly "relative to Edg-4 and Edg-2 receptors" (claims 13 and 18); "the modulator exhibits at least about 20 fold inhibitor activity selectivity for Edg-7 relative to other Edg receptors" (claim 9); "the biological activity is cell proliferation" (claim 14); "cell proliferation leads to cancer selected from the group consisting of ovarian cancer, peritoneal cancer..." (claim 19); "cell proliferation is stimulated by LPA" (claim 20); "the biological activity is selected from the group consisting of calcium mobilization, VEGF synthesis, IL-8 synthesis, platelet activation..." (claim 21); "the modulator binds to the Edg-7 receptor with a binding constant of at least about 10 nM" (claim 22); "the modulator binds to the Edg-7 receptor with binding constant between about 100 fM and 1μM" (claim 23); "the modulator is an organic molecule of molecular weight of less than 750 daltons" (claim 24); and "the cell is selected from the group consisting of a hepatoma cell, a ovarian cell, an epithelial cell..." (claim 26).

Honn teaches use of the claimed compound represented by the formula (I) such as compound 126 (commonly known as nimodipine) in combination with platinum compound (e.g., cisplantin) for the treatment of malignant tumors in vitro and in vivo including head and

neck, ovarian, testicular, bladder and colon cancers (entire documents, especially column 13, lines 4-6; claims 1 and 3).

Although Honn is silent about the claimed specific selective inhibitory activity of Edg-7 receptor, the stimulation of cell by LPA, the specific binding constant and "an organic molecule of molecular weight of less than 750 daltons", such properties or characteristics deem to be inherent to the referenced method.

The prior art directing the administration of compound inherently possessing a therapeutic effect for the same ultimate purpose as disclosed by applicant anticipates applicant's claims even absent explicit recitations of the mechanism of action. As discussed above, the prior art does not disclose the underlying pharmacological mechanism of "modulating Edg-7 receptor mediated biological activity...". However, the fact that the applicant may have discovered a new pharmacological mechanism for nimodipine is not considered patentably distinctive over the prior art which are directed to the same therapeutic application (e.g., for the treatment of ovarian cancer, colon cancer, bladder cancer, etc...).

With respect to the combination with "one or more agonist or antagonists of an Edg-7 receptor" (claim 31), since the interpretation of the instant claim allows for the inclusion of both of edg-7 receptors as being identical to each other, the reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Honn et al. (USP 4906646), and further in view of Bible et al. (Clinical Cancer Research, Vol. 6, 661, February 2000, pp. 661-670)

The teaching of Honn has been discussed in above 102(b) rejection.

The teaching of Honn differs from the instant invention in the specific cells selected from "OV202 human ovarian cell, a HTC rat hepatoma cell, a CAOV-3 human ovarian cancer cell,

MDA-MB-453 breast cancer cell, MDA-MB-231 breast cancer cell, HUVEC cells, A 431 human epitheloid carcinoma cell and a HT-1080 human fibrosarcoma cell".

Bible is being supplied as reference to demonstrate the state of art knowledge in selecting suitable cell lines such as OV202 human ovarian cell in vitro test of chemotherapeutic agent.

Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

14. Claims 29-32 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 29-32 of copending Application No. 10/760002. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

15. Claims 29-30 and 32 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 29-30 and 32 of copending Application No. 10/760003, 29-30 and 32 of copending Application No. 10/760064, 29-30 and 32 of copending Application No. 10/760063

or 29-30 and 32 of copending Application No. 10/759992. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

16. Claims 1-2, 4, 14, 17-21 and 25-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2, 4, 14, 19-21 and 25-27 of copending Application No. 10/760064. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claimed invention overlaps with the copending application. The prior art directing the administration of the same compound(s) inherently possessing a therapeutic effect for the same ultimate purpose as disclosed by applicant anticipates applicant's claims even absent explicit recitations of the mechanism of action. Thus, the reference makes obvious the instant invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

17. No Claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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PRIMARY EXAMINER